(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 773 025 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
14.05.1997 Bulletin 1997/20

(21) Application number: **96901349.9**

(22) Date of filing: **26.01.1996**

(51) Int. Cl.[6]: **A61K 31/44**, A61K 9/50

(86) International application number:
PCT/ES96/00013

(87) International publication number:
WO 96/23500 (08.08.1996 Gazette 1996/36)

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB IE IT LI NL PT SE
Designated Extension States:
SI

(30) Priority: **01.02.1995 ES 9500181**

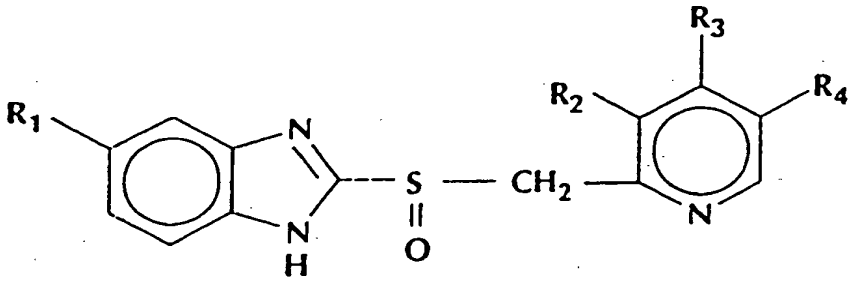
(71) Applicant: **ESTEVE QUIMICA, S.A.**
08024 Barcelona (ES)

(72) Inventors:
- **BALLESTER RODES, Montserrat**
  E-08023 Barcelona (ES)
- **VAN BOVEN, Marinus**
  E-08391 Tiana (ES)

(74) Representative: **SUGRANES - VERDONCES - FERREGÜELA**
Calle Provenza, 304
08008 Barcelona (ES)

(54) NEW STABLE GALENIC FORMULATIONS CONTAINING AN ACID-LABILE BENZIMIDAZOL COMPOUND, AND PRODUCTION PROCESS

(57) New stable galenic formulations containing an acid-labile benzimidazol compound, and production process. Said formulations comprise a neutral nucleus on which is applied a layer containing the active ingredient and comprised of the benzimidazol compound having the general formula (I), a water-soluble polymer and non-alkaline reaction vehicles, and on which is applied a second isolating layer which comprises a water-soluble polymer, a pigment and talcum, and a last enteric layer which contains a polymer, a plastifier and talcum.



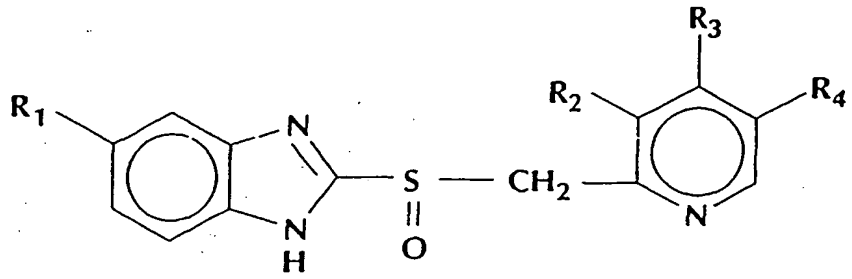
(I)

EP 0 773 025 A1

Description

Field of the invention

The present invention is related to new stable pharmaceutical preparations for oral administration containing a 2[(2-pyridyl)methylsulphinyl]-benzimidazole derivative (hereinafter referred to as "benzimidazole compound") of formula I:



wherein R_1 is hydrogen, methoxy or difluoromethoxy, R_2 is methyl or methoxy, R_3 is methoxy, 2,2,2,-trifluoroethoxy or 3-methoxypropoxy, R_4 is hydrogen or methyl.

The invention also relates to a method for the manufacture of such preparations aid to a method for the treatment of gastrointestinal diseases.

Background of the invention

The above benzimidazole compounds are very effective drugs for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease, severe erosive esophagitis, Zollinger-Ellison syndrome and H-pylori eradication. However, it is well known that these compounds have poor stability. In the solid state they are susceptible to heat, moisture and light, and in aqueous solution or suspension their stability decreases with decreasing pH. The degradation of these compounds is catalyzed by acidic reacting compounds.

Pharmaceutical preparations containing acid-labile compounds have to be subcoated in order to avoid a reaction between the active ingredient and the outer acidic enteric coating which reaction -if occurring- would result in degradation, destabilisation and consequently discolouration of the active ingredient.

The use of a barrier layer to protect the pharmaceutical from degradation caused by an enteric coating is well known from the prior art. Nevertheless, it is not possible to use conventional enteric coatings in a conventional way for acid labile benzimidazole compounds since decomposition takes place and the preparations become discoloured and lose in the active ingredient content with time. Prior art partially avoids the above mentioned stability problem by including an alkaline salt form of the benzimidazole compound or incorporating an alkaline reacting compound into an enteric coated preparation (magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, composite aluminium/magnesium compounds, sodium lauryl sulfate, aminoacids, N-methyl-D-glucamine, etc.) as described in US-A-4,786,505, US-A-5,232,706, EP-A-237200, EP-A-124495, US-A-5,385,739, EP-A-519144, the alkaline reacting compound being present within or on the surface of the nucleus together with the benzimidazole compound. Some authors use the alkaline reacting compound also in the composition of a second isolation layer to ensure stability of these forms. It is important to note that patent US-A-4,786,505, in its Example 1, Table 1 No.1, illustrates a formulation which is free of such alkaline compound and it is shown in Table 3 (No. 1-II) that this formulation has a rather poor stability. Thus, the association of an alkaline substance to the neutral form of the benzimidazole compound is tought in order to improve the stability of the active compound, especially for solid dosage forms, and enteric coating is recommended. That is, according to the state of the art, the addition of an alkaline substance to the pharmaceutical preparation is required to ensure the stability of the drug for long term storage.

Outline of the invention

According to the present invention high stability solid preparations containing a benzimidazole compound of formula I are obtained. The new galenic formulations do not contain alkaline reacting compounds; thus, an alkaline reacting compound is not present in the enteric coated preparation of the invention. Surprisingly, the obtained new preparations have a significantly enhanced stability for long-term storage, much higher than the known preparations, avoiding discolouration and loss of purity, thus being more suitable for pharmaceutical use.

The new preparation is characterized in that to an inert sugar/starch spherical core, a first layer is applied containing a mixture of the benzimidazole compound of formula I as active ingredient, a water soluble inert polymer and non-

alkaline reacting pharmaceutical acceptable excipients, followed by a second isolation layer formed by water soluble polymers and compatible excipients. Finally a third layer consisting of an enteric coating is applied. The core, the process conditions and the excipients have been selected in order to obtain the required coating efficiency for each layer.

The resulting new preparation is resistant to dissolution in acid media being stable for passage through the gastric juice, and dissolves rapidly in a neutral to alkaline media, the conditions in the proximal part of the small intestine. In fact, the acid resistance, tested as per US Pharmacopoeia, demonstrated that after 2 hours the total amount of the benzimidazole remained intact and that upon changing the pH to 6,8, after 30 minutes all the benzimidazole was dissolved (tested as per US Pharmacopoeia).

Detailed description of the invention

In a fluidized bed apparatus, uniform spherical inert cores (composition as per US Pharmacopoeia) are coated with a first layer consisting of the acid labile benzimidazole compound, an inert water soluble polymer such as hydroxy-propylmethylcellulose or hydroxypropylcellulose, and talc. The second layer consists of an inert water soluble polymer such as hydroxypropylmethylcellulose or hydroxpropylcellulose, talc and a pigment such as titanium dioxide. The third and enteric coating layer consists of an enteric coating polymer such as co-polymerized methacrylic acid / methacrylic acid methyl esters, a plasticizer such as triethylcitrate or similar plasticizers, and talc.

The layers are applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions.

The active ingredients can be administered in the same dosages and according to the same protocol as the corresponding already marketed commercial dosage forms.

For oral administration, the final dosage may take the form of capsules containing the pellets, or pellets compressed into a tablet.

The dose as the benzimidazole compound lies within the range of about 1 mg to 100 mg/kg/day, adjusted to individual patients needs and for as long as clinically indicated.

The invention is described in detail in the following examples:

Example 1

In 3440 g of deionized water 436 g of omeprazole (I; R_1=-OCH_3, R_2=CH_3, R_3=-OCH_3, R_4=CH_3), 444 g of hydroxypropylmethylcellulose and 118 g of talc are dispersed.

3010 g of inert uniform sugar/starch spheres (composition according to US Pharmacopoeia) are introduced into a fluidized bed apparatus and the previous obtained dispersion is sprayed on the spheres. After spraying, the spheres are dried before applying the second layer.

In 2365 g of deionized water, 355 g of hydroxypropylmethylcellulose, 43 g or talc and 43 g of titanium dioxide are dispersed and the resulting aqueous dispersion is sprayed on the spheres obtained in the previous step. After spraying, the spheres are dried before applying the third enteric coating layer.

In 1890 g of deionized water, 1950 g of methacrylic acid copolymer (US Pharmacopoeia, type C aqueous dispersion), 98 g of triethylcitrate and 98 g of talc are dispersed, and the resulting aqueous dispersion is sprayed on the spheres obtained in the previous step. After applying this final enteric coating layer the spheres (pellets) are dried.

The pellets thus obtained were stored in closed polyethylene bags within a closed cardboard fibre container and also in closed glass containers and submitted to so called accelerated conditions, that is 40°C and 75% relative humidity. At the same time pellets obtained from Prilosec® capsules (Merck/Astra trademark) were stored in identical containers and submitted to the same conditions. The results of the test under accelerated conditions are summarized in tables 1, 2 and 3. They demonstrate a superior stability over the already authorized product on the market.

TABLE 1

COLOR OF THE PELLETS			
	AT THE START	1 MONTH	3 MONTHS
Pellets (I) - Fiber container	A	A	D
Pellets (I) - Glass container	A	A	B
Prilosec - Fiber container	A	C	F
Prilosec - Glass container	A	A	E

A : White
B : Pinkish white
C : faint brown
D : light brown
E : brown
F : Deep brown

TABLE 2

OMEPRAZOLE PURITY *			
	AT THE START	1 MONTH	3 MONTHS
Pellets (I) - Fiber container	99,5%	98,8%	52%
Pellets (I) - Glass container	99,5%	98,7%	97,9%
Prilosec - Fiber container	96,1%	85,2%	1%
Prilosec - Glass container	96,1%	96,2%	1%

* Analyzed as per HPLC, described in Pharmaeuropa, Vol. 4, n° 2, June 1992 and expressed as direct area percentage.

TABLE 3

OMEPRAZOLE RECOVERY AFTER US DISSOLUTION TEST		
	1 MONTH	3 MONTHS
Pellets (I) - Fiber container	96,8%	9,2%
Pellets (I) - Glass container	99,9%	73,8%
Prilosec - Fiber container	21,3%	<< 1%
Prilosec - Glass container	84,5%	<< 1%

Example 2

In 580 g of deionized water, 75 g of lansoprazole (I; R_1=H, R_2=CH_3, R_3= 2,2,2-trifluoroethoxy, R_4=H), 70 g of hydroxypropylmethylcellulose and 18,5 g of talc are dispersed.

490 g of inert uniform sugar/starch spheres are introduced into a fluidized bed apparatus and the previous obtained dispersion is sprayed on the spheres. The process continues in the same manner as in Example 1 spraying the second layer and the third enteric coating layer. These two dispersions have the following composition:

Second layer: 350 g of deionized water, 52 g of hydroxypropylmethylcellulose, 7 g of talc and 7 g of titanium dioxide.

Enteric coating layer: 280 g of deionized water, 290 g of a USP methacrylic acid copolymer (type C aqueous suspension), 13 g of triethylcitrate and 13 g of talc.

The pellets obtained were stable and showed a similar profile as the ones from example 1.

Biopharmaceutical studies

The purpose of the study was to investigate the bioavailability and pharmacokinetic profile of the newly developed formulation of omeprazole in comparison with the standard capsule formulation (Prilosec®; 20 mg).

Hard gelatin capsules were filled with the new galenic form of omeprazole, prepared according to example 1, in an amount corresponding to 20 mg of omeprazole.

The experimental design was a single center, open-label, randomized, 2-way cross-over study in 24 healthy male and female subjects.

Subjects reported to the clinical unit at about 8 p.m. in the evening prior to the day of treatment, and they remained hospitalized until 12 hours after drug intake. Subjects received a standard meal the evening before dosing.

The drug was given in the clinical unit with 200 ml of tap water after subjects had been fasting for at least 10 hours.

The concentration of omeprazole in blood plasma was assayed by a validated high pressure liquid chromatography method with UV detection (Internal Report No. CPR 95-742). The mean plasma concentrations are given in Table 4.

TABLE 4

The mean plasma concentrations (ng/ml) after 20 mg oral doses of omeprazole new formulation given as capsules *vs.* Prilosec® capsules.		
Time (h.)	New formulation	Prilosec®
Baseline	0,0	0,0
0,5	16,4	6,3
1,0	103,7	105,4
1,5	161,8	191,9
2,0	192,0	210,1
2,5	165,4	168,4
3,0	132,7	119,8
3,5	103,8	87,6
4,0	81,4	63,5
5,0	39,7	47,2
6,0	14,9	22,0
7,0	8,1	9,5
8,0	5,4	5,7
12,0	0,0	2,3

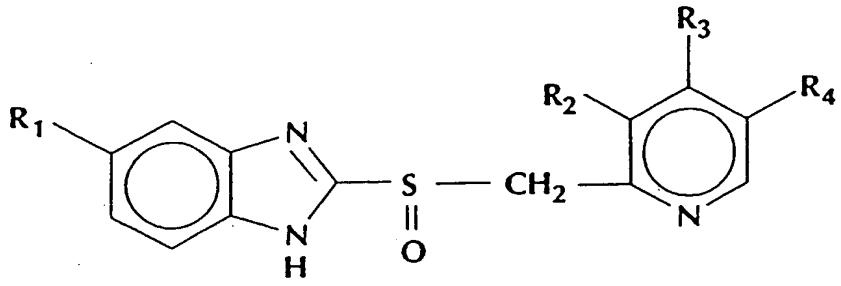
The pharmacokinetic results for omeprazole were comparable with those reported in the literature (Wilde MI, McTavish D. Omeprazole. An update of its pharmacology and therapeutic use in acid related disorders. Drugs 1994, 48: 91-132). The arithmetic mean (SD) half-lives of elimination of omeprazole were 0,9 (0,4) and 1,1 (0,7) h after oral administration of the new and Prilosec® formulation, respectively. The arithmetic mean (SD) T_{max} values of omeprazole were 2,3 (1,0) and 2,0 (1,1) h after administration of the new and Prilosec® formulation, respectively. The corresponding values for the geometric mean of the maximum plasma concentration C_{max} were 249 (197) and 241 (174) ng/ml, and those of $AUC_{0-\infty}$ were 434 (440) and 486 (436) ng h/ml, respectively.

The ratios of geometric means (new/Prilosec®) of C_{max} and AUC were 1,03 in both cases, and the 2-side 90% confidence intervals (CI) for these ratios were entirely within the interval 0,80 - 1,25. According to the CPMP guidance for bioequivalence studies, bioequivalence of the formulations (new formulation and Prilosec® formulation) can be accepted (References: CPMP Working Party on the Efficacy of Medicinal Products 1991. Note for guidance: Investigation of bioavailability and bioequivalence; Schulz HU, Steinijans VW. Striving for standards in bioequivalence assessment: A review; Int. J. Clin. Pharmacol. Ther. Toxicol. 1992, 30 (suppl.1): S1-S6).

Thus, by preparing omeprazole capsules according to the present invention, it is possible to obtain a preparation with the same bioavailability as the Prilosec® capsules containing the same amount of micronized active compound.

Claims

1. A stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I:



wherein R_1 is hydrogen, methoxy or difluoromethoxy, R_2 is methyl or methoxy, R_3 is methoxy, 2,2,2,-trifluoroethoxy or 3-methoxypropoxy, R_4 is hydrogen or methyl, which comprises:

(a) a nucleus formed by an inert core, the acid labile benzimidazole, an inert water soluble polymer and non-alkaline reacting pharmaceutical acceptable excipients;
(b) an inert coating disposed on said nucleus, formed by a water soluble polymer and other pharmaceutical acceptable excipients;
(c) an outer layer disposed on the previous coating comprising an enteric coating.

2. A preparation according to claim 1 wherein the water soluble polymer comprises hydroxypropylmethylcellulose or hydroxypropylcellulose.

3. A preparation according to claim 1 wherein the enteric coating comprises a gastric resistant polymer such as copolymerized methacrylic acid / methacrylic acid methyl esters, a plasticizer such as triethylcitrate, and pharmaceutical acceptable excipients.

4. A process for the preparation of a stable oral pharmaceutical preparation containing an acid labile benzimidazole compound of formula I as active ingredient, which comprises: preparing a nucleus formed by an inert core covered by a layer that contains the acid labile benzimidazole, an inert water soluble polymer comprising hydroxypropylmethylcellulose or hydroxypropylcellulose and non-alkaline reacting pharmaceutical acceptable excipients; coating said nucleus with an inert layer formed by a water soluble polymer also comprising hydroxypropylmethylcellulose or hydroxypropylcellulose, and other pharmaceutical acceptable excipients; and finally coating the previous coating with an enteric coating which comprises a gastric resistant polymer such as copolymerized methacrylic acid / methacrylic acid methyl ester, a plasticizer such as triethylcitrate, and pharmaceutical acceptable excipients.

5. A galenic preparation in the form of capsules or tablets containing the stable oral pharmaceutical preparation according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES 96/00013

A. CLASSIFICATION OF SUBJECT MATTER

IPC6 A61K 31/44 A61K 9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6 A61K .

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0519365 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK) 23.12.92 see claims 1-3 see examples 1,2 see column 3, line 4 - line 9	1-5
X	EP 0519144 A (ILSAN ILAC VE HAMMADDELERI SANAYI) 23.12.92 see claims 1-5 see page2, line 39 - line 58 see page 3, line 1 - line 26	1,2,5

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 1996 (21.05.96)	31 May 1996 (31.05.96)
Name and mailing address of the ISA/ OEPM Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)